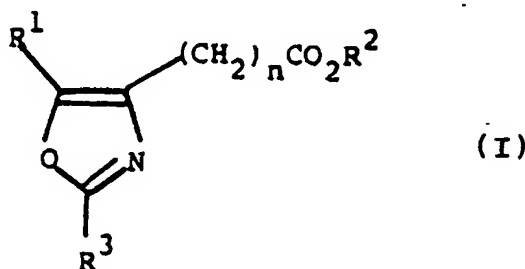




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁴ : A61K 31/42, C07D 263/32</p>	<p>A1</p>	<p>(11) International Publication Number: WO 87/ 03807 (43) International Publication Date: 2 July 1987 (02.07.87)</p>
<p>(21) International Application Number: PCT/GB86/00789 (22) International Filing Date: 22 December 1986 (22.12.86) (31) Priority Application Number: 8531608 (32) Priority Date: 23 December 1985 (23.12.85) (33) Priority Country: GB (71) Applicant (for all designated States except US): BEECHAM GROUP P.L.C. [GB/GB]; Beecham House, Great West Road, Brentford, Middlesex TW8 9BD (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : HINDLEY, Richard, Mark [GB/GB]; Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).</p>		<p>(74) Agents: JONES, Pauline et al.; Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, NL (European patent), US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: **OXAZOLE DERIVATIVES AND THEIR USE AS ANTI-HYPERGLYCAEMIC**



(57) Abstract

A method for the treatment and/or prophylaxis of hyperglycaemia in humans or non-human mammals, which method comprises the administration of an effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or amide thereof, wherein R¹ represents a C₁₋₆ alkyl, C₁₋₆ alkylaryl or aryl group; R² represents a hydrogen atom or a C₁₋₆ alkyl group; R³ represents a substituted or unsubstituted aryl group; and n represents an integer of from 1 to 6; and certain compounds and pharmaceutical compositions for use in such method.

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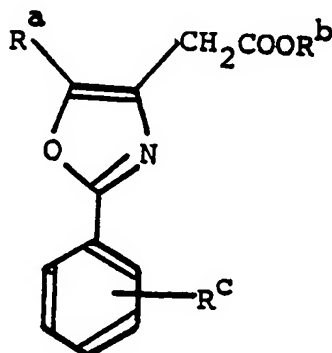
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Oxazole derivatives and their use as anti-hyperglycaemic.

The invention relates to a method for the treatment and/or prophylaxis of hyperglycaemia and compounds for use in such method.

Japanese Published Application No. 0051111 discloses oxazoles of formula (A):



(A)

or salts thereof, wherein

R^a = lower alkyl,

R^b = H or lower alkyl,

R^c = H or halogen.

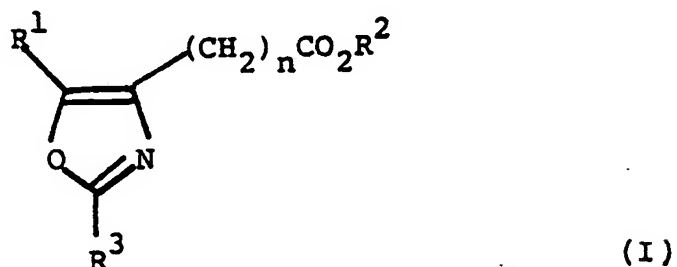
The oxazoles of formula (A) and salts thereof are disclosed as having good serum-cholesterol and serum-triglyceride level lowering activity and good platelet-agglutination inhibitory activity, being useful as anti-lipaemic agents.

It has now surprisingly been discovered that certain oxazoles, including the compounds of formula (A), have useful anti hyperglycaemic activity.

Accordingly, the present invention provides a method for the treatment and/or prophylaxis of hyperglycaemia

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in humans or non-human mammals, which method comprises the administration of an effective, non-toxic amount of a compound of formula (I):



or a pharmaceutically acceptable salt ester or amide thereof, wherein

R^1 represents a C_{1-6} alkyl, C_{1-6} arylalkyl or aryl group;

R^2 represents a hydrogen atom or a C_{1-6} alkyl group;

R^3 represents a substituted or unsubstituted aryl group; and

n represents an integer of from 1 to 6.

When R^1 represents an aryl group it is suitably a phenyl group.

When R^3 represents an aryl group it is suitably a phenyl group, preferably substituted with up to two halogen atoms.

Favourably, n represents an integer of from 1 to 4, preferably 1, 2 or 3.

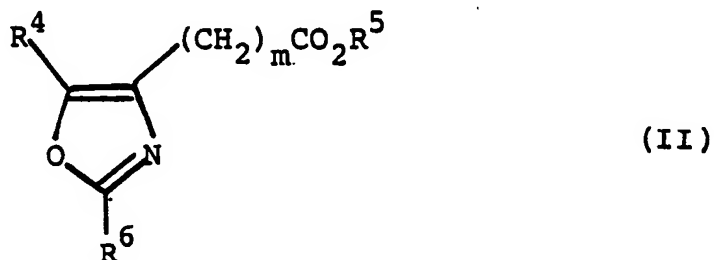
In a further aspect, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt, ester or amide thereof, for use in the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia in humans or non-human mammals.

The present invention also provides a pharmaceutical composition for use in the treatment and/or prophylaxis

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of hyperglycaemia in humans or non-human mammals which comprises an effective, non-toxic amount of a compound of formula (I), or a pharmaceutically acceptable salt, ester or amide thereof, and a pharmaceutically acceptable carrier therefor.

Certain of the compounds of formula (I) are novel compounds, accordingly the present invention provides a compound of formula (II):



or a pharmaceutically acceptable salt, ester or amide thereof, wherein

R^4 represents a C_{1-6} alkyl, C_{1-6} arylalkyl or aryl group;

R^5 represents a hydrogen atom or a C_{1-6} alkyl group;

R^6 represents a substituted or unsubstituted aryl group; and

m represents an integer of from 1 to 6; providing that when R^4 represents lower alkyl, R^5 represents a hydrogen atom or lower alkyl and m represents 1; then R^6 does not represent a phenyl group or a phenyl group substituted with a halogen atom.

When R^4 represents an aryl group it is suitably a phenyl group.

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When R^6 represents an aryl group it is suitably a phenyl group substituted with up to two halogen atoms. Preferably, R^3 or R^6 represent 4-chlorophenyl or 2,4-dichlorophenyl.

Preferably, R^1 or R^4 represents a group selected from the group consisting of: methyl, ethyl, n-propyl or phenyl.

Preferably, R^2 or R^5 represent a methyl group.

Suitable aryl groups, or aryl moieties as for example in the C_{1-6} alkylaryl group, include substituted or unsubstituted phenyl or naphthyl groups.

Suitably, when substituted the aryl group may be substituted with up to five, favourably up to three, groups selected from halogen, C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, halo C_{1-6} alkyl, hydroxy, amino, nitro, carboxy C_{1-6} alkoxy carbonyl, C_{1-6} alkyl carbonyloxy or C_{1-6} alkyl carbonyl groups.

When used herein the term 'lower alkyl' relates to C_{1-6} alkyl groups.

When used herein the term ' C_{1-6} alkyl' or the term ' C_{1-6} alk' relate to the groups or moieties comprising straight and branched chain alkyl groups containing from 1 to 6 carbon atoms, such as methyl, ethyl, propyl and butyl.

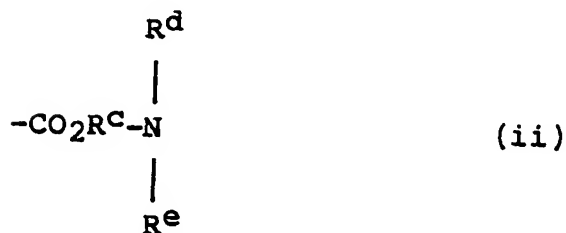
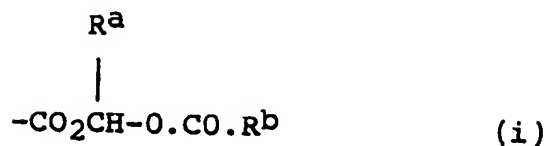
When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine, preferably chlorine.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium

or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl) -amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

Suitable pharmaceutically acceptable esters of carboxy groups are in-vivo hydrolysable esters.

Examples of suitable pharmaceutically acceptable in vivo hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those of part formula (i), (ii) and (iii):



wherein

R^a is hydrogen, methyl, or phenyl,

R^b is C₁₋₆ alkyl, C₁₋₆ alkoxy or phenyl; or

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R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;

R^c represents C₁₋₆ alkylene optionally substituted with a methyl or ethyl group -

R^d and R^e independently represent C₁₋₆ alkyl;

R^f represents C₁₋₆ alkyl.

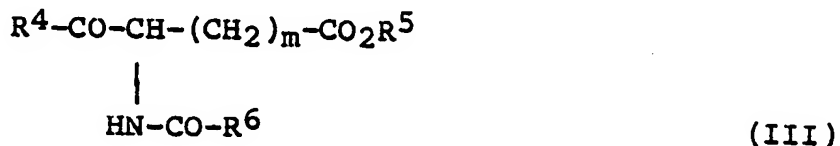
Examples of suitable in vivo hydrolysable ester group include for example acyloxyalkyl groups such as acetoxymethyl, pivaloyloxy-methyl, α -acetoxylethyl and α -pivaloyloxyethyl groups; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyl-oxymethyl and α -ethoxycarbonyloxyethyl; dialkylamino-alkyl especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl and lactone groups such as phthalidyl and dimethoxyphthalidyl.

Suitable acid addition salts of compound (I) or (II), when comprising an amino group, include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, α -keto glutarate, α -glycerophosphate, and glucose-1-phosphate. Preferably the acid addition salt is a hemisuccinate, hydrochloride, α -ketoglutarate, α -glycerophosphate or glucose-1-phosphate, in particular the hydrochloride salt.

Suitable pharmaceutically acceptable amides are amides of formula CO.NR^sR^t wherein R^s and R^t each independently represent hydrogen or C₁₋₆ alkyl or R^s

and R^t together with the nitrogen atom to which they are attached form a 5- or 6- membered ring.

The present invention also provides a process for the preparation of compounds of formula (II), or a pharmaceutically acceptable salt, ester or amide thereof, which process comprises cyclising a compound of formula (III):



wherein R⁴, R⁵, R⁶ and m are as defined in relation to formula (II); and thereafter if necessary carrying out one or more of the following steps:

- (i) converting a compound of formula (II) into another compound of formula (II);
- (ii) converting a compound of formula (II) into a pharmaceutically acceptable salt, ester or amide thereof.

Suitably, the cyclisation of the compound of formula (II) is carried out in the presence of a dehydrating agent, such as phosphoryl chloride.

The compounds of formula (I) may be prepared by an analogous process to that used to prepare compounds of formula (II).

The abovementioned reaction is suitably carried out in toluene, or any other suitable solvent, at any convenient temperature, preferably at an elevated

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temperature such as the refluxing temperature of the chosen solvent.

The compounds of formula (III) are either known compounds or may be prepared using processes analogous to those used to prepare known compounds, for example by using the processes disclosed in Japanese Published Application No. 51111. The methods disclosed therein may also be used to prepare compounds of formula (I) or (II).

The present invention further provides a compound of the general formula (II), or pharmaceutically acceptable salt, ester or amide thereof, for use in the treatment of hyperglycaemia in human or non-human mammals.

A compound of the general formula (I) or (II), or a pharmaceutically acceptable salt thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

In a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the general formula (II), or a pharmaceutically acceptable salt, ester or amide thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

The administration to the human or non-human mammal may be by way of oral administration or parenteral administration.

Preferably, the compound of formula (I) or (II) (hereinafter called 'the drug') is administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition. Such unit doses will normally comprise 0.1 to 1000 mg of the drug, more usually 0.1 to 550 mg.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable

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disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the drug and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

In treating hyperglycaemic humans the drug may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be about 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In treating hyperglycaemic in mammals, especially dogs, the drug may be administered by mouth, usually once or twice a day and at about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg.

The following physiological data and Examples illustrate the invention, but do not limit it in any way.

EXAMPLE 1

Methyl 2-(4-chlorophenyl)-5-methyl-4-oxazolyl-acetate

To a solution of methyl 3-(4-chlorobenzamido)-4-oxo-pentanoate (6.5 g) in toluene (100 ml) was added phosphoryl chloride (5 ml) and the mixture was boiled under reflux with vigorous stirring with exclusion of moisture for 5
5 hours. The solvent was evaporated, the residue dissolved in dichloromethane (100 ml), washed successively with saturated sodium carbonate solution (2 x 100 ml) and saturated brine (100 ml), dried (MgSO₄) and evaporated. The oil thus obtained was purified by chromatography on
10 silica gel in 1% methanol-dichloromethane to give the title compound, m.p. 59-60°C (hexane-diethyl ether).

¹H nmr δ(CDCl₃)

2.38 (3H,s); 3.56 (2H,s); 3.75 (3H,s); 7.4 (2H,d); 7.9 (2H,d).

EXAMPLE 2

Methyl 2-(4-chlorophenyl)-5-phenyl-4-oxazolyl-acetate

The title compound, mp. 112-113°C, was prepared from methyl 3-(4-chlorobenzamido)-3-benzoylpropionate in a similar manner to that described in Example 1.

¹H nmr δ(CDCl₃)

5 3.75 (3H,s); 3.85 (2H,s); 7.2-7.8 (7H, complex); 8.05 (2H,d).

EXAMPLE 3

Methyl 2-(4-chlorophenyl)-5-n-propyl-4-oxazolyl-acetate

The title compound, mp. 73-74°C (ether-hexane) was prepared from methyl 3-(4-chlorobenzamido)-4-oxoheptanoate in a similar manner to that described in Example 1.

¹H nmr δ(CDCl₃)

- 5 1.0 (3H,t); 1.4-1.9 (2H,m); 2.65 (2H,t); 3.55 (2H,s);
 3.85 (3H,s); 7.4 (2H,d); 7.95 (2H,d).

EXAMPLE 4

Methyl [3-(2-(4-chlorophenyl)-5-methyl-4-oxazolyl)propionate

The title compound, mp. 66-67°C (hexane) was prepared from methyl-4-(4-chlorobenzamido)-5-oxohexanoate in a similar manner to that described in Example 1.

¹H nmr δ(CDCl₃)

5 2.30 (3H,s); 2.75 (4H, complex); 3.65 (3H,s); 7.35 (2H,d);
7.9 (2H,d).

EXAMPLE 5

Methyl [3-(2-(4-chlorophenyl)-5-ethyl-4-oxazolyl)propionate

The title compound, mp. 42-45°C (hexane), was prepared from methyl-4-(4-chlorobenzamido)-5-oxoheptanoate in a similar manner to that described in Example 1.

¹H nmr δ(CDCl₃)

- 5 1.25 (3H,t); 2.55-2.9 (6H, complex); 3.65 (3H,s); 7.4 (2H, d); 7.85 (2H,d) .

EXAMPLE 6

Methyl [3-(2-(2,4-dichlorophenyl)-5-methyl-4-oxazolyl)]
propionate

The title compound, mp. 78-80°C (diethylether-hexane), was prepared from methyl-4-(2,4-dichlorobenzamido)-5-oxohexanoate in a similar manner to that described in Example 1.

^1H nmr δ (CDCl_3)

- 5 2.35 (3H,s); 2.75 (4H, complex); 3.75 (3H,s); 7.15-7.5
 (2H, complex); 7.85 (2H,d).

BIOLOGICAL DATA

Diabetic Mice, Mid-day Blood Glucose Concentrations

C57Bl/KsJ diabetic (db/db) female mice, 5-6 weeks old, were housed 5 per cage and fed on a powdered rat and mouse breeders diet (H.C. Styles, Bewdley, Worcs.) for one week. At the end of this period, blood samples were obtained at mid-day for the determination of blood glucose in all mice. The animals then continued to receive the powdered diet or were given the powdered diet supplemented with the test compound. After 7 days, the blood glucose concentration at mid-day were again determined.

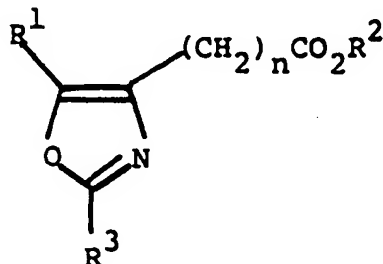
The results of the determination of mid-day blood glucose concentrations taken at the end of each treatment are shown below as the mean (mM). The comparable values for animals fed on the powdered diet alone are also shown as controls. Five mice (i.e. one cage of mice) were used on each treatment.

<u>Test</u>			<u>Dose</u>
<u>Compound</u>	<u>Control</u>	<u>Treated</u>	<u>(mmol kg⁻¹ of diet)</u>
Example 1	19.9	9.6	6
Example 2	22.3	12.0	9
Example 5	21.0	6.6	6
Example 6	28.2	7.0	6

No adverse toxicological effects were indicated in the above tests.

Claims

1. A method for the treatment and/or prophylaxis of hyperglycaemia in humans or non-human mammals, which method comprises the administration of an effective, non-toxic amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, ester or amide thereof, wherein

R¹ represents a C₁₋₆ alkyl, C₁₋₆ arylalkyl or aryl group;

R² represents a hydrogen atom or a C₁₋₆ alkyl group;

R³ represents a substituted or unsubstituted aryl group; and

n represents an integer of from 1 to 6.

2. A method according to claim 1, wherein R¹ represents a phenyl group.

3. A method according to claim 1 or claim 2, wherein R³ represents a phenyl group, preferably substituted with up to the two halogen atoms.

4. A method according to any one of claims 1 to 3, wherein n represents an integer of from 1 to 4, preferably 1, 2 or 3.

5. A method according to claim 1, wherein the compound of formula (I) is selected from the list consisting of:

methyl 2-(4-chlorophenyl)-5-methyl-4-oxazolyl-acetate;

methyl 2-(4-chlorophenyl)-5-phenyl-4-oxazolyl-acetate;

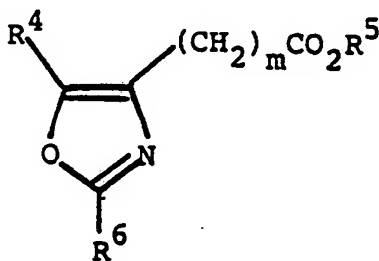
methyl 2-(4-chlorophenyl)-5-n-propyl-4-oxazolyl-acetate;

methyl [3-(2-(4-chlorophenyl)-5-methyl-4-oxazolyl)]-propionate;

methyl [3-(2-(4-chlorophenyl)-5-ethyl-4-oxazolyl)]-propionate; and

methyl [3-(2-(2,4-dichlorophenyl)-5-methyl-4-oxazolyl)]propionate.

6. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt, ester or amide thereof, wherein

R⁴ represents a C₁₋₆ alkyl, C₁₋₆ arylalkyl or aryl group;

R⁵ represents a hydrogen atom or a C₁₋₆ alkyl group;

R⁶ represents a substituted or unsubstituted aryl group; and

m represents an integer of from 1 to 6; providing that when R⁴ represents lower alkyl, R⁵ represents a hydrogen atom or lower alkyl and m represents 1; then R⁶ does not represent a phenyl group or a phenyl group substituted with a halogen atom.

7. A compound according to claim 6, wherein R⁴ represents a phenyl group.

8. A compound according to claim 6 or claim 7, wherein R⁶ represents 4-chlorophenyl or 2,4-dichlorophenyl.

9. A compound according to any one of claims 6 to 8, wherein R⁴ represents methyl, ethyl, n-propyl or phenyl.

10. A compound according to any one of claims 6 to 9, wherein R⁵ represents methyl.

11. A compound according to claim 6, selected from the list consisting of:

methyl 2-(4-chlorophenyl)-5-methyl-4-oxazolyl-acetate;

methyl 2-(4-chlorophenyl)-5-phenyl-4-oxazolyl-acetate;

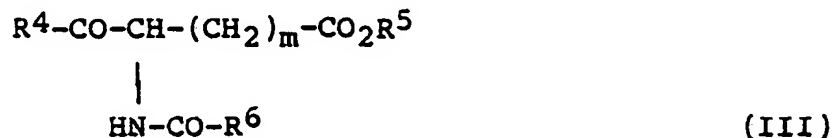
methyl 2-(4-chlorophenyl)-5-n-propyl-4-oxazolyl-acetate;

methyl [3-(2-(4-chlorophenyl)-5-methyl-4-oxazolyl)]-propionate;

methyl [3-(2-(4-chlorophenyl)-5-ethyl-4-oxazolyl)]-propionate; and

methyl [3-(2-(2,4-dichlorophenyl)-5-methyl-4-oxazolyl)]propionate.

12. A process for the preparation of a compound of formula (II), which process comprises cyclising a compound of formula (III):



wherein R^4 , R^5 , R^6 and m are as defined in relation to formula (II); and thereafter if necessary carrying out one or more of the following steps:

- (i) converting a compound of formula (II) into another compound of formula (II);
- (ii) converting a compound of formula (II) into a pharmaceutically acceptable salt, ester or amide thereof.

13. A pharmaceutical composition comprising a compound of the general formula (II) and a pharmaceutically acceptable carrier therefor.

14. A compound of the general formula (II), or pharmaceutically acceptable salt thereof, for use in the treatment of hyperglycaemia in human or non-human mammals.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB·86/00789

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: A 61 K 31/42; C 07 D 263/32

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System

Classification Symbols

IPC⁴

A 61 K 31/00; C 07 D 263/00

Documentation Searched other than Minimum Documentation
to the extent that such Documents are included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X, Y	EP, A, 0094612 (TANABE SEIYAKU CO. LTD) 23 November 1983, see claims --	6-14
Y	EP, A, 0096890 (TAKEDA CHEMICAL) 28 December 1983, see claims; page 1, lines 19-23 --	6, 12-14
A	EP, A, 0092239 (TAKEDA CHEMICAL) 26 December 1983, see claims 1, 4; page 1, lines 15-19 -----	6, 12-14

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

13th March 1987

Date of Mailing of this International Search Report

24 APR 1987

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

M. VAN MOL

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1-5, because they relate to subject matter not required to be searched by this Authority, namely:

See Rule 39.1(iv) PCT

Methods for treatment of the human or animal body by therapy.

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 27/03/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0094612	23/11/83	JP-A- 58201771	24/11/83
		US-A- 4535089	13/08/85
EP-A- 0096890	28/12/83	JP-A- 58219169	20/12/83
		AU-A- 1565783	22/12/83
		CA-A- 1195986	29/10/85
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		US-A- 4596816	24/06/86